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(54) Title: AQUEOUS TOPICAL COMPOSITIONS COMPRISING KOJIC ACID, SALICYLIC ACID AND A WATER SOLUBLE GLYCOL ETHER

(57) Abstract

Disclosed is an aqueous topical composition for skin lightening comprising: (a) a safe and effective amount of kojic acid, (b) a safe and effective amount of salicylic acid, (c) water, and (d) from about 20 % to about 30 % by weight of the composition, of a water soluble glycol ether of the general formula $R^1–O–[(CH_2)_mO]_nH$; wherein R^1 is an alkyl of 1 to 6 carbon atoms, m is from about 2 to about 3, and n is from about 1 to about 2; wherein said composition has a pH from about 2.5 to about 4, and is absent of a thickener. Also disclosed is a method for lightening mammalian skin comprising topically applying to the skin said aqueous topical composition.

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AQUEOUS TOPICAL COMPOSITIONS COMPRISING KOJIC ACID, SALICYLIC ACID AND A WATER SOLUBLE GLYCOL ETHER

TECHNICAL FIELD

The present invention relates to an aqueous topical compositions such as lotions, toners, and astringents comprising kojic acid, salicylic acid and a water soluble glycol ether which is useful for lightening of mammalian skin.

BACKGROUND OF THE INVENTION

Skin lightening is an important skin care need, especially in the Asian population. This includes overall lightening of basal skin tone and hyperpigmented lesions. It is generally known that conditions which result in defective or missing tyrosinase, an enzyme involved in the formation of melanin, lead to a loss of pigmentation, e.g. albinism. Conversely, it is known that inhibition of tyrosinase leads to skin lightening via inhibition of melanogenesis. See King, R. A. and C. G. Summers, Dermatologic Clinics, Vol. 6 pp. 217-227 (1988).

Tyrosinase is present within the melanosomes in epidermal melanocytes and catalyzes the formation of melanin from tyrosine. See Goldsmith, L. A., Physiology, Biochemistry, and Molecular Biology of the Skin, Oxford University Press, pp. 873-903 (N.Y. 1991). Binding of an inhibitor to the active site of tyrosinase results in decreased melanin formation. See generally Prota, G. Melanins and Melanogenesis, Academic Press, Inc., (San Diego 1992).

The art has produced certain tyrosinase inhibitors. However, it is well recognized in the art that any active in any composition, especially when used for topical application (whether for pharmaceutical or cosmetic purposes) must be efficacious, bioavailable, stable when exposed to light, air or to the skin. Should the product be unstable, the breakdown products of the active must be innocuous.

One known tyrosinase inhibitor is kojic acid. Kojic acid has been found to be quite useful for topical skin lightening compositions. Unfortunately, kojic acid is quite expensive. In addition, kojic acid does not have an exfoliation effect.

One solution to add exfoliation effect on kojic acid is the addition of salicylic acid to the topical composition. Salicylic acid is commonly used in topical compositions because of its exfoliation effects. When combined with kojic acid, salicylic acid exfoliates mammalian skin which results in improving removal effect of skin pigmentation. An example of such a topical skin lightening composition is found in Japanese Patent Laid-open (KOKAI) No. 7-300404. The costs of such a composition, however, are still quite high due primarily to the amount and costs of kojic acid. Consequently, there is a need for an economical composition comprising kojic acid which efficaciously lightens mammalian skin.

SUMMARY

The present invention relates to an aqueous topical composition for skin lightening comprising:

(a) a safe and effective amount of kojic acid,

(b) a safe and effective amount of salicylic acid,

(c) water, and

(d) from about 20% to about 30% by weight of the composition, of a water soluble glycol ether of the general formula: R^1-O-[$(CH_2)_mO]_nH$; wherein R^1 is an alkyl of 1 to 6 carbon atoms, m is from about 2 to about 3, and n is from about 1 to about 2;

wherein said composition has a pH from about 2.5 to about 4, and is absent of thickeners.

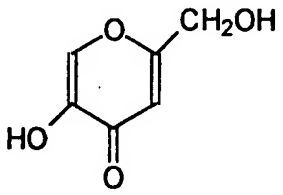
The composition of the present invention provides an aqueous topical composition without thickener which is useful for lightening of mammalian skin. The composition enhances the penetration of kojic acid to mammalian skin. By the excellent penetration effect of kojic acid to mammalian skin, the composition has excellent lightening effect for mammalian skin, yet requires lower levels of kojic acid than previously believed necessary. The reduced level of kojic acid results in a significant cost savings.

DETAIL DESCRIPTION

All percentages and ratios are based on weight, and all measurements are conducted at 25 °C, unless otherwise specified.

A. KOJIC ACID

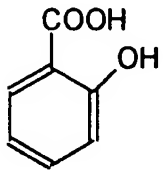
The composition of the present invention comprises a safe and effective amount of kojic acid. Kojic acid which is 5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one is a well known active component and is described in the Merck Index, eleventh edition, page 838 (1989). The structure of kojic acid is as follows:



Kojic acid is used as a skin lightening ingredient to inhibit formation of melanin. If the composition comprises more than about 3% by weight of the composition, of kojic acid, it is not economical, and if it comprises less than about 0.5% by weight of the composition, of kojic acid, enough skin lightening effect is not expected. Typically, the composition of the present invention comprises from about 0.5% to about 3%, preferably from about 1% to about 2% by weight of the composition, of kojic acid.

B. SALICYLIC ACID

The composition of the present invention comprises a safe and effective amount of salicylic acid. Salicylic acid which is 2-hydroxybenzoic acid is a well known active component and is described in the Merck Index, eleventh edition, page 1324 (1989). The structure of salicylic acid is as follows:



Salicylic acid is used to exfoliate mammalian skin and to enhance penetration of kojic acid to mammalian skin. If the composition comprises more than about 2% by weight of the composition, of salicylic acid, it will cause irritation, and if it comprises less than about 1% by weight of the composition, of salicylic acid, enough exfoliation effect and enough penetration enhancing effect is not expected. Typically, the composition of the present invention comprises from about 1% to about 2%, preferably from about 1.2% to about 1.5% by weight of the composition, of salicylic acid.

C. WATER

The composition of the present invention comprises water. Water is used as a solvent. If the composition comprises more than 78.5% by weight of the composition, of water, other ingredients which are required in the present invention cannot be included, and if the composition comprises less than 40% by weight of the composition, of water, it is not economical. Typically, the composition of the present invention comprises from about 40% to about 78.5%, preferably from about 45% to about 70% by weight of the composition, of water.

D. WATER SOLUBLE GLYCOL ETHER

The composition of the present invention comprises water soluble glycol ether.

Water soluble glycol ether can be characterized by the general formula:

R^1-O-[$(CH_2)_mO$]$_n$H; wherein R^1 is an alkyl of 1 to 6 carbon atoms, m is from about 2 to about 3, and n is from about 1 to about 2. Examples of the alkyl group R^1 include methyl, ethyl, propyl, butyl and hexyl groups. This glycol ether having a diethylene group as the alkylene group and ethyl group as the alkyl moiety is diethyleneglycol monoethyl ether which has been given the CTFA (The Cosmetic, Toiletry and Fragrance Association) designation ethoxydiglycol. Preferred water soluble glycol ether are diethyleneglycol monoethyl ether which is commercially available by the tradename TRANSCUTOL from Gattefosse, France; diethyleneglycol monomethyl ether; and dipropyleneglycol monomethyl ether and the more preferred water soluble glycol ether is diethyleneglycol monoethyl ether.

Water soluble glycol ether is used as a solvent of salicylic acid and to aid enhancing penetration of kojic acid to mammalian skin. If the composition comprises more than about 30% of water soluble glycol ether, enough penetration effect of kojic acid is not expected, it is not mild enough to skin and it is not economical, and if the composition comprises less than 20% of water soluble glycol ether, salicylic acid cannot be dissolved in it.

Typically the water soluble glycol ether is included in the composition in amounts from about 20% to about 30%, preferably from about 23% to about 27% by weight of the composition, of water soluble glycol ether.

E. OPTIONAL COMPONENTS

The aqueous topical composition of the present invention can optionally comprise one or more components which are commonly used in such topical compositions. Examples of such optional components are discussed in more detail below.

However, it is an important aspect of the invention that thickeners not be present in the composition because it decreases the penetration effect of kojic acid to mammalian skin. Thickeners means ingredients which are commonly used to increase the viscosity of cosmetics. The thickeners include natural, semi-synthetic and synthetic types. Natural thickeners include gum arabic, traganth, carrageenan, xanthan gum, gelatin and sodium chondroitin sulfate. Semi-synthetic thickeners include methyl cellulose, carboxymethyl cellulose, sodium nitro cellulose, ethyl cellulose, hydroxy ethyl cellulose, hydroxy methyl cellulose, hydroxy propyl cellulose, rice starch, wheat starch, sodium alginate and propylene glycol alginate. Synthetic thickeners include polyvinyl alcohol, polyvinyl pyrrolidone, poly (vinyl acetate), sodium polyacrylate, polyacrylic resin, alkanolamine solution, poly (ethyl methacrylate), carboxyvinyl polymer, poly(ethylene glycol) and copolymer of polyoxyethylene and polyoxypropylene.

It is also an important aspect of the invention that after all of the optional components are added, the composition preferably have a pH from about 2.5 to about 4, preferably a pH from about 3 to about 4. If pH is more than 4, preferred exfoliation effect of salicylic acid and preferred skin lightening effect of kojic acid cannot be expected, and if pH is less than 2.5, it will cause skin damage.

Examples of optional compositions which may be used in the present invention include the following.

1. Polyhydric alcohol and lower alcohols having 1 to 3 carbons

Polyhydric alcohol is used as a moisturizer. If the composition comprises more than about 15% of polyhydric alcohol, it is not economical, and causes safety issues, and if it comprises less than about 2%, the moisturizing effect is not expected.

Compositions of this invention can optionally comprise from about 2% to about 15%, preferably from about 3% to about 10% by weight of the composition, of polyhydric alcohols

such as propylene glycol, hexylene glycol, glycerin, and propane diol. Among the polyhydric alcohol, glycerin is preferred.

Lower alcohols having 1 to 3 carbons can be used to impart a refreshing feel or cool sensation to the skin. If the composition comprises more than about 15% of the lower alcohols, it will cause irritation, and if the composition comprises less than about 2% of the lower alcohols, the refreshing feel and cool sensation effect is not expected.

Compositions of this invention can optionally comprise from about 2% to about 15%, preferably from about 3% to about 10% by weight of the composition, of lower alcohols having 1 to 3 carbons such as ethanol and isopropanol

Among the lower alcohols having 1 to 3 carbons, ethanol is preferred.

Ethanol is preferably comprised upon making compositions which are designed to impart a refreshing feel or cool sensation to the skin. It is known that ethanol in the composition helps improve solubility of salicylic acid. This level of ethanol is expected to provide the desired refreshing feel to skin without being irritating or excessively drying to the skin.

2. Nonionic surfactant

Nonionic surfactant is used to aid dissolving other ingredients. If the composition comprises more than about 5% of nonionic surfactant, it is not economical and may cause safety issues, and if it comprises less than about 1% of nonionic surfactant, the effect to aid dissolving other ingredients is not expected.

Compositions of this invention can optionally comprise from about 1% to about 5%, preferably from about 2% to about 4% by weight of the composition, of a nonionic surfactant. The nonionic surfactant acts as a co-solubilizer of salicylic acid, thereby allowing higher salicylic acid level when using the same solvent. Nonionic surfactants useful herein include any of the well-known nonionic surfactants that have an HLB (hydrophile-lipophile balance) from about 10 to about 18, preferably from about 12 to 16.

Non-limiting examples of these nonionic surfactants are ethoxylated or propoxylated, preferably ethoxylated, alcohols and alkyl phenols with alcohol derivatives preferred. In general, these alcohol derivatives contain a straight or branched chain alkyl group having 8-22 carbons, preferably 10-20 carbons, more preferably 12-20 carbons, and generally contain from about 6 to about 30, preferably from about 8 to about 25, ethylene oxide or propylene oxide groups. Among these ethoxylated and propoxylated alcohols, the ethoxylated derivatives are preferred.

Preferred for use herein are polyethylene oxide ethers derived from lauryl alcohol, cetyl alcohol, oleyl alcohol, stearyl alcohol, isocetyl or isostearyl alcohol and mixtures thereof. Most preferred for use herein is isocetyl ether condensed with an average of 20 moles of ethylene oxide, known by CTFA designation as Isoceteth 20 (hereinafter called Isocetech 20).

3. Dialkylpolysiloxane-polyoxyalkylene copolymer

Compositions of this invention can optionally comprise a dialkylpolysiloxane-polyoxyalkylene copolymer. Such a copolymer is expected to improve the overall skin feel imparted by the composition and to reduce any irritation which might be caused by a component of the present invention. If the composition comprises more than about 5% of dialkylpolysiloxane-polyoxyalkylene copolymer, it is not economical and may cause safety issues, and if it comprises less than about 1% of dialkylpolysiloxane-polyoxyalkylene copolymer, the effect of improving overall skin is not expected. The composition preferably comprises from about 1% to about 5% of dialkylpolysiloxane - polyoxyalkylene copolymer, most preferably from about 2% to about 4% dialkylpolysiloxane - polyoxyalkylene copolymer.

Dialkylpolysiloxane - polyoxyalkylene copolymers useful herein include those which are soluble in water. Dimethylpolysiloxane-polyoxyalkylene copolymers, known as Dimethicone copolyols where the polyoxyalkylene group can be a polyoxyethylene or a polyoxypropylene group or a combination of both, are particularly useful. The dimethylpolysiloxane portion is typically made of from 10 to about 30 units, preferably around 15 to 20 units. The polyalkylene portion is typically made of from 8 to about 12, preferably from 10 to about 12 units.

4. Sunscreens, conditioning agents, vitamins, perfumes, etc.

Other optional components can be included in the aqueous topical compositions of the present invention, depending on the needs of the product. Non-limiting examples of such optional components include water-soluble additional surfactants to aid solubility of the composition, water-soluble ultraviolet and infrared screening and absorbing agents to screen and absorb ultraviolet and infrared, water-soluble anti-inflammatory agents to reduce inflammation, water-soluble anti-oxidant/radical scavenging agents to control oxidation and scavenge radical, water-soluble chelating agents to chelate metal, water-soluble skin conditioning agents to condition skin, water-soluble perfume for preference, water-soluble color for preference, water-soluble pH adjusters for adjusting pH, water-soluble dyes for preference, water-soluble vitamins to condition skin, water-soluble proteins to condition skin, water-soluble plant extracts to condition skin, and water-soluble nutrients to condition skin.

For the sake of preventing the composition comprising kojic acid from colouring, a composition of the present invention can include at least one anti-colouring agent selected from the group consisting of sodium metabisulfite, sodium bisulfite and sodium sulfite.

A wide variety of acids, bases, buffers, and sequestrants can be utilized to adjust and/or maintain the pH and ionic strength of the compositions useful in the present invention. Materials useful for adjusting and/or maintaining the pH and/or the ionic strength include sodium carbonate, sodium hydroxide, hydrochloric acid, phosphoric acid, sulfuric acid, acetic acid, sodium acetate, sodium hydrogen phosphate, sodium dihydrogen phosphate, citric acid,

sodium citrate, sodium bicarbonate, triethanolamine, EDTA (ethylenediaminetetraacetic acid), disodium EDTA, tetrasodium EDTA, and the like.

The compositions of the present invention are typically formulated to have a pH from about 2.5 to about 4, preferably a pH from about 3 to about 4.

The aqueous topical compositions of the present invention include lotions, toners and astringents.

F. METHODS FOR LIGHTENING SKIN IN MAMMALS

The present invention also relates to methods for skin lightening in mammals comprising topical application of the skin lightening composition of the present invention. The amount of active agent and frequency of application will vary widely depending upon the skin color already in existence in the subject, the rate of further darkening of the skin, and the level of lightening desired.

A safe and effective amount of skin lightening agent in a topical composition is applied, generally from about 1 mg to about 10 mg per cm^2 skin per application, preferably from about 2 mg to about 8 mg/ cm^2 skin per application, more preferably from about 3 mg to about 7 mg/cm^2 skin, also preferably from about 4 mg to about 5 mg/cm^2 skin. Application preferably ranges from about four times a day to about twice a week, more preferably from about three times a day to about once every other day, more preferably still from about once daily to about twice daily. Application for at least five days is required to see a skin lightening effect in lower animals. Application for at least one month is required to see an effect in humans. After lightening is achieved, the frequency and dosage can be reduced to a maintenance level, as desired. Such maintenance varies according to the individual, but is preferably from about 1/10 to about 1/2, more preferably from about 1/5 to about 1/3 of the original dosage and/or frequency, as needed.

The following examples further describe and demonstrate the preferred embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration, and are not to be construed as limitations of the present invention since many variations thereof are possible without departing from its spirit and scope.

G. EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention. All percentages are based on weight.

Example compositions numbers 1-4 are shown in Table 1, below.

Table 1

Examples
(Amount in weight %)

Component	No.1	No.2	No.3	No.4
Kojic acid	1	1	1.5	2
Salicylic acid	1.5	1.2	1.5	1.5
TRANSCUTOL*	25	23	25	27
Sodium citrate	4.5	3	4.5	4.5
Citric acid	6	4	6	6
Glycerin	3	0	3	5
Sodium metabisulfite	0.25	0.25	0.25	0.25
0.01% D&C yellow #10	0.3	0	0.03	0
Isoceteth 20	0	1	3	4
Dimethicone copolyol	0	1	3	4
water	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100
pH	3.4	3-4	3-4	3-4

* TRANSCUTOL is diethyleneglycol monoethyl ether which is commercially available from Gattefosse, France.

The compositions shown in Table 1 can be prepared by any conventional method well known in the art. An example of a suitable preparing method which may be used is described as follows:

Preparing method of Example No. 1

Salicylic acid and TRANSCUTOL are combined and heated to about 70-75 °C. Separately, glycerin, sodium citrate, citric acid and water are mixed together to obtain water phase-I. Water phase-I is also mixed at about 70-75 °C. The salicylic acid/TRANSCUTOL mixture is then slowly added to water phase-I and mixed at 75 °C for 30 minutes to obtain mixture-1. Kojic acid, sodium metabisulfite and water are mixed together to obtain water phase-II. Water phase-II is also mixed at 45 °C. Then water phase-II and D&C yellow #10 are also added to mixture-1 to obtain a lotion.

Preparing method of Example No. 2

Salicylic acid and TRANSCUTOL are combined and heated to about 70-75 °C. Separately, sodium citrate, citric acid, Isoceteth 20 and water are mixed together to obtain water phase-I. Water phase-I is also mixed at about 70-75 °C. The salicylic acid/TRANSCUTOL mixture is then slowly added to water phase-I and mixed at 75 °C for 30 minutes to obtain a lotion.

Kojic acid, sodium metabisulfite, dimethicone copolyol and water are mixed together to obtain water phase-II. Water phase-II is also mixed at 45 °C. Then water phase-II is also added to mixture-1 to obtain a lotion.

Preparing method of Example No. 3

Salicylic acid and TRANSCUTOL are combined and heated to about 70-75 °C. Separately, glycerin, sodium citrate, citric acid, Isocetech 20 and water are mixed together to obtain water phase-I. Water phase-I is also mixed at about 70-75 °C. The salicylic acid/TRANSCUTOL mixture is then slowly added to water phase-I and mixed at 75 °C for 30 minutes to obtain mixture-1. Kojic acid, sodium metabisulfite, dimethicone copolyol and water are mixed together to obtain water phase-II. Water phase-II is also mixed at 45 °C. Then water phase-II and D&C yellow #10 are also added to mixture-1 to obtain a lotion.

Preparing method of Example No. 4

Salicylic acid and TRANSCUTOL are combined and heated to about 70-75 °C. Separately, glycerin, sodium citrate, citric acid, Isoceteth 20 and water are mixed together to obtain water phase-I. Water phase-I is also mixed at about 70-75 °C. The salicylic acid/TRANSCUTOL mixture is then slowly added to the water phase-I and mixed at 75 °C for 30 minutes to obtain mixture-1. Kojic acid, sodium metabisulfite, dimethicone copolyol and water are mixed together to obtain water phase-II. Water phase-II is also mixed at 45 °C. Then water phase-II is also added to mixture-1 to obtain a lotion.

The compositions of the present invention have improved skin penetration enhancing effect of kojic acid compared versus compositions which comprise thickener and/or comprise more than about 30% by weight of the composition, of water soluble glycol ether. A strong lightening effect of mammalian skin will be obtained by the compositions of the present invention, due to the resulting strong skin penetration enhancing effect of kojic acid.

Example No. 5

This example sets forth a method for lightening mammalian skin using a composition of the present invention.

The composition of example No. 1 is applied 5 mg / cm^2 skin per application three times a day for one month. After one month, a significant skin lightening effect is seen. Once the desired level of the skin lightening is achieved, treatment is reduced to limit a day, to maintain the level of lightening.

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to one skilled in the art and are to be included in the spirit and purview of this application and scope of the appended claims.

What is claimed is:

1. An aqueous topical composition for skin lightening comprising:
   (a) a safe and effective amount of kojic acid,
   (b) a safe and effective amount of salicylic acid,
   (c) water, and
   (d) from about 20% to about 30% by weight of the composition, of a water soluble glycol ether of general formula:

   R^1-O-[$(CH_2)_m$O]$_n$H; wherein R^1 is an alkyl of 1 to 6 carbon atoms, m is from about 2 to about 3, and n is from about 1 to about 2;

   wherein said composition has a pH from about 2.5 to about 4, and is absent of a thickener.

2. The aqueous topical composition according to claim 1 comprising from about 0.5% to about 3% by weight of the composition, of kojic acid; from about 1% to about 2% by weight of the composition, of salicylic acid; and from about 40% to about 78.5% by weight of the composition, of water.

3. The aqueous topical composition according to claim 1 comprising from about 1% to about 2% by weight of the composition, of kojic acid; from about 1.2% to about 1.5% by weight of the composition, of salicylic acid; and from about 40% to about 78.5% by weight of the composition, of water.

4. The aqueous topical composition according to claim 1 comprising:
   (a) from about 1% to about 2% by weight of the composition, of kojic acid;
   (b) from about 1.2% to about 1.5% by weight of the composition, of salicylic acid;
   (c) from about 40% to about 78.5% by weight of the composition, of water; and
   (d) from about 23% to about 27% by weight of the composition, of water soluble glycol ether

   wherein said composition has a pH from about 3 to about 4.

5. The aqueous topical composition according to claim 4 wherein said water soluble glycol ether is diethylene glycol monoethyl ether.

6. The aqueous topical composition according to claim 4 wherein said aqueous topical composition is a lotion.

7. The aqueous topical composition according to claim 4 further comprising at least one anti-colouring agent selcted from the group consisiting of sodium metabisulfite, sodium bisulfite and sodium sulfite.

8. A method for lightening mammalian skin comprising topically applying to the skin said aqueous topical composiiton of claim 1.

9. A method for lightening mammalian skin comprising topically applying to the skin said aqueous topical composition of claim 4.

10. A method for enhancing penetration of kojic acid to mammalian skin comprising topically applying to the skin said aqueous topical composition of claim 4.

INTERNATIONAL SEARCH REPORT

Intern. nal Application No
PCT/US 96/16942

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 680 748 A (L'OREAL) 8 November 1995 see claims 1,22; examples 2,5 ---	1,8
A	EP 0 661 038 A (L'OREAL) 5 July 1995 see claims 1,18; examples 1,2 ---	1,8
A	EP 0 661 035 A (L'OREAL) 5 July 1995 see claims 1,20; example 1 ---	1,8
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
29 May 1997	17. 06. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Voyiazoglou, D

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INTERNATIONAL SEARCH REPORT

Intern. ial Application No
PCT/US 96/16942

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